

# ERdj2 Promotes Hepatocellular Carcinoma Metastasis

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## Abstract

Tumor cells display augmented capability to keep endoplasmic reticulum (ER) homeostasis under microenvironmental stimuli. Metabolic reprogramming is a well-known hallmark for tumor cells to provide specific adaptive traits to the microenvironmental alterations. However, it's unknown how tumor cells orchestrate metabolic reprogramming and tumor progression to keep ER homeostasis. We identified ERdj2 as a new regulator of HCC cell metastasis. IHC staining revealed that high expression of ERdj2 predicted unfavorable prognosis of HCC patients and HCC metastasis. Mechanistically, the phosphorylation of ERdj2 at T537 by IRE1 $\alpha$  pathway contributed to ERdj2 activation. Then, the stability of ACLY was upregulated by ERdj2 to increase the supply of acetyl-CoA and lipid biosynthesis, which are beneficial for improving ER capacity. Meanwhile, ERdj2 also entered nucleus for increasing nuclear acetyl-CoA production to upregulate unfolded protein response targets to improve ER homeostasis. Importantly, ERdj2 coordinated with ACLY to epigenetically modulate expression of Snail1 in the nucleus. Consequently, ERdj2 promoted HCC cell metastasis and these effects were reversed by ACLY inhibition.

## Keywords

ERdj2, Hepatocellular Carcinoma, Metastasis, ER Stress, Metabolic Reprogramming